Reliable and General Method for the Cleavage of α-Arylheteroatom-Substituted Carboxylic Acids

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Abstract: Bonds between arylheteroatom moieties and α-carbons of carboxylic acids are efficiently cleft by azide transfer and subsequent Curtius rearrangement. The scope of the one-pot protocol covers differently substituted carboxylic acids and heteroatoms like O, S, Se, and N.

Key words: azides, cleavage, carboxylic acids, arenes, rearrangement

Aryloxy acetates exhibit an extraordinary stability towards electrophilic conditions,[1] since the strong electron-withdrawing effect of the carbonyl group onto the methylene moiety avoids a heterolytic cleavage with a positive charge on the methylene group. Therefore, typical electrophilic conditions for the dealkylation of phenylethers do not affect this particular moiety,[2] whereas a methoxy group undergoes such a cleavage in a smooth manner.[3] Furthermore, aryloxy acetates are a common motif in plant-growth modulators,[4] which exhibit also a high metabolic stability.[5] The alkoxycarbonylmethyl group represents a recognition site for some electrophilic reagents and can consequently be exploited for side-chain-directed transformations, e.g., the direct chlorination of iodo arenes by $MoCl_5$.[1a]

In order to circumvent the very drastic reaction conditions[6] for a chemical cleavage of aryloxy acetates we developed a mild strategy.[7] The one-pot method consists of an azide transfer with a subsequent Curtius rearrangement followed by a hydrolytic workup. The initial protocol was limited to about 60% yield for an individual cleavage. The mild conditions even gave access to labile iodo phenols, but for multiple deprotection sequences the loss of material is unacceptable. The ameliorated procedure employs diethylphosphoryl azide (DEPA)[8] instead of diphenylphosphoryl azide (DPPA)[9] as azide-transfer reagent and glycerol as additive in the hydrolytic workup.[10] The cleavage is then compatible to a broad scope of *O*-carboxymethyl-substituted phenols and is performed in excellent yields.[11] We found that this methodology has a more general nature than previously described.

The employed acids have been prepared by known procedures or analogously.[15] In general, the ester was synthesized followed by saponification which provided the acid upon workup. The deprotected compounds **2** (Figure 1) were identical in all aspects with the commercially available compounds.[16]

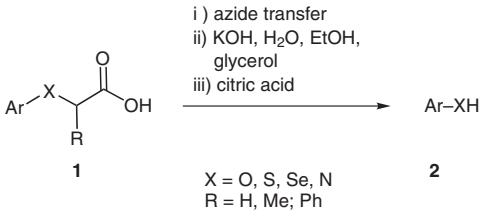

Figure 1 Cleavage of α-arylheteroatom-substituted carboxylic acids

Since *O*-alkoxycarbonylmethyl-protected phenols are superb substrates for the $MoCl_5$-mediated aryl coupling reaction,[1b] chiral analogues were subjected to the deprotection sequence. First, we focussed on substrates derived from naturally occurring α-hydroxy acids like lactic or mandelic acids. These substrates were prepared according to standard procedures.[17] The lactic acid derivative is liberated to the corresponding 2,4-dichlorophenol in 91% yield (Table 1, entry 1). Analogous mandelic acid derivatives can also be cleft in good to excellent yields (Table 1, entries 2 and 3). The more polar and volatile 4-chlorothymol renders a slightly depressed yield because of the workup conditions. In order to demonstrate the generality of this deprotection sequence we subjected substrates with other heteroatoms than oxygen. A variety of anilines were tested but lead to low yields since the workup seems to be inappropriate. Therefore, more lipophilic amides can serve as substrates to remove a *N*-glycine moiety in moderate yield (Table 1, entry 4). The displacement of the carboxymethyl group from the nitrogen atom of carbazole was achieved in significantly better yields (Table 1, entry 5). However, addition of glycerol on a later stage in the workup turns out to be beneficial in order to avoid side reactions.

The protocol was tested on the sulfur congeners of phenoxyacetates. A variety of thiophenol derivatives (**1f–h**) were deprotected by the original protocol using DPPA. Because of the volatility and sensibility towards atmospheric conditions, the thiophenols were oxidized to the corresponding disulfides by iodine upon the workup (Table 1, entry 6–8). The substitution pattern on the thiophenol does not have an obvious impact on the yield.

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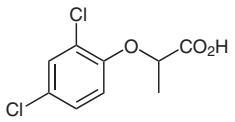
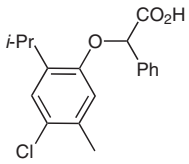
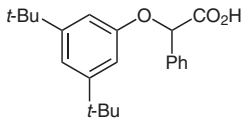
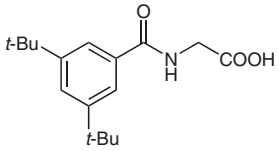
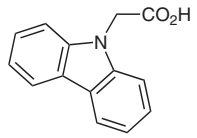
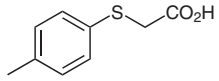
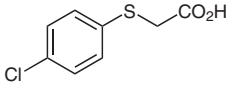
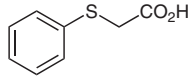
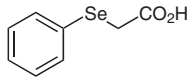
Table 1 Cleavage of Heteroatom–α-Carbon Bond[a]

Entry	Substrate	Azide-transfer reagent	Yield (%)[b]
1	 **1a**[12]	DEPA	91
2	 **1b**	DEPA	96
3	 **1c**	DEPA	99
4	 **1d**	DEPA	46
5	 **1e**	DEPA	66[d]
6	 **1f**[13]	DPPA	73[c]
7	 **1g**[13]	DPPA	88[c]
8	 **1h**[13]	DPPA	65[c]
9	 **1i**[14]	DEPA	93

[a] *Reagents and conditions*: i) **1**, DEPA or DPPA, Et_3N, DMF, toluene, 30 min, 25 °C, then 3 h reflux, ii) glycerol, KOH/H_2O, EtOH, 2 h reflux; iii) citric acid, H_2O.
[b] Isolated yields.
[c] During workup, iodine (0.51 equiv) was added. Yield corresponds to disulfides.
[d] Glycerol was added after 1.5 h reflux with EtOH, KOH/H_2O.

Additionally, the sequence was applied to the corresponding selenium derivative; the phenyl selenol was isolated in excellent yield (Table 1, entry 9).

In conclusion, the removal of carboxy methyl fragments from various heteroatoms can be achieved by a one-pot sequence including azide transfer, Curtius rearrangement, and hydrolytic workup. The general and reliable method is applicable to heteroatoms like O, N, S, and Se. Furthermore, α-substituted carboxylic acids like lactic and mandelic acid are splendid substrates for this reaction sequence. In particular, these chiral auxiliaries can be envisioned for an asymmetric biaryl formation when the appropriate reagent is direct by this specific side chain.

Acknowledgment

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References and Notes

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(10) **General Procedure for the Cleavage Sequence**
The substrate (0.60 mmol) is dissolved in anhyd toluene (1.5 mL) and anhyd DMF (0.15 mL). After addition of Et_3N (1.01 equiv) and azide-transfer reagent (1.1 equiv, DPPA or DEPA) the mixture was stirred for 30 min at ambient temperature and then brought to reflux for 3 h. Then, KOH solution (0.7 mL, 50 wt% in H_2O), EtOH (1.5 mL), and glycerol (0.8 mL) were added to the reaction mixture before refluxing for 2 h. For workup, the reaction mixture was brought to pH 5 by the addition of a sat. citric acid solution. Subsequently, the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions are washed two times with brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification was performed by column chromatography.

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